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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/536,768

05/27/2005

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EXAMINER

SAUCIER, SANDRA E

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/536,768	Applicant(s) TAOKA ET AL.	
	Examiner Sandra Saucier	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-12 and 14-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-12 and 14-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 7-12, 14-26 are pending and are considered on the merits.

A proposed examiner's amendment was offered to applicants by fax to applicants' attorney on 5/12/08. The offer was declined and is hereby rescinded. Continuing examination on the merits follows.

Specification

The examiner thanks the applicant for drawing attention to the present rules for claiming priority and for national stage examination under 35 USC 371.

Priority

Applicants state that the claim for priority is proper since 12/6/03 was a Saturday and the next appropriate day was Monday, 12/8/02 and this statement is accepted by the examiner.

Claim Rejections – 35 USC § 112

Claims 14-16, 23, 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At least some of the claims require one of ordinary skill in the art to have access to a specific microorganism. Because the microorganism is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the microorganism is not so obtainable or available, the requirements of 35 USC 112 may be satisfied by deposit of the microorganism. The specification does not disclose a repeatable process to obtain the microorganism and it is not clear from the specification or record that the microorganism is readily available to the public.

The objection and accompanying rejection may be overcome by

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establishing that each microorganism identified is readily available to the public and will continue to be so for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer, or by an acceptable deposit as set forth herein. See 37 CFR 1.801–1.809. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or a statement by an attorney of record over his/her signature and registration number, stating that the deposit has been made under the Budapest Treaty and that all restrictions imposed by the depositor on availability to the public of the deposited material will be irrevocably removed upon issuance of the patent would satisfy the deposit requirement. See 37 CFR 1.808.

If the deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria, assurance must be provided to the effect that:

- (1) during the pendency of the application, access to the cultures will be made available to one determined by the Commissioner to be entitled thereto;
- (2) any restrictions on availability of the deposits to the public will be irrevocably removed upon the granting of a patent;
- (3) the deposits will be maintained for a term of at least of 30 years from the date of deposit and at least 5 years after the last request for the material;
- (4) a viability statement in accordance with the provisions of 37 CFR 1.807; and
- (5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Assurance may be provided in the form of an affidavit, declaration or averment under oath or by a statement of the attorney of record over her or his signature and registration number.

The specification must also state the date of deposit, the number granted by the depository and the name and address of the depository. See 37 CFR 1.803–1.809 for additional explanation of

these requirements.

For example, FERM BP-6898 does not have a statement assuring irrevocable removal of restrictions on availability to the public.

Claims 7-12, 14-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite on multiple occasions the phrase "represented by the general formula". This renders the claims indefinite because it is unclear how "general" the formula may be or to what extent the formula may vary and still be considered to fall within the description of "general".

Claims 10, 12, 14-16, 23, 26 are indefinite because they recite the use of a "cultured product" or "processed product" of a recombinant microbe. It is unclear what the metes and bounds of these recitations are. For example, does it mean the culture medium or an isolated enzyme from the microbe or include some other meanings. In the absence of a definition, it is unclear what these terms encompass.

Claims 7-12, 14-16 do not have a recovery step for the compound produced.

The claims are incomplete in the absence of a recovery step for the product produced. While there is no specific rule or statutory requirement which specifically addresses the need for a recovery step in a process of preparing a composition, it is clear from the record and would be expected from conventional preparation processes that the product must be isolated or recovered. Thus, the claims fail to particularly point out and distinctly claim the "Complete" process since the recovery step is missing from the claims. The metes and bounds of the claimed process are therefore not clearly established or delineated.

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Claim Rejections – 35 USC § 102/103

Claims 7, 8, 11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by, or in the alternative, under 35 U.S.C. 103(a) obvious over US 4,734,367 [A] in light of Barth *et al.* [U].

The claims are directed to a method for making optically active 3-hydroxy-2-substituted-propionic acid esters comprising: subjecting 2-formylacetic acid ester of formula 2 to a reduction catalyzed by an enzymatic source from various genera.

US 4,734,367 demonstrates a stereoselective fermentative reduction of 2-formylacetic acid ester to (R) or (S) 3-hydroxy-2-substituted propionic acid. Microbes used are preferably aerobic or facultative aerobic yeasts, fungi or bacteria (col. 1, l. 68) and claim 1, preferred microbes belong to the genus *Candida* and other preferred genera, table column 2.

Barth *et al.* disclose that a microbe belonging to the genus *Yarrowia* has been also classified as belonging to the genus *Candida* by those of skill in the art (abstract).

Some microbes belonging to the genus *Candida* have been reclassified as *Yarrowia*. Therefore, because of the cross classification of these microbes by those of skill in the art, use of the microbes from the genus *Yarrowia* to effect the instant biotransformation is considered to be the same as or so closely related as to be obvious over transformation by microbes from the genus *Candida* which is clearly a preferred genus in the cited prior art to produce preponderantly either the (R) or the (S) isomer by reduction of the compound of formula 2.

Claims 7, 8, 9 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by, or in the alternative, under 35 U.S.C. 103(a) obvious over US 4,734,367 [A] in light of the ATCC Catalog of Bacteria and Bacteriophages [V].

The claims are directed to the stereoselective reduction of the compound of formula 2 by microbes from *Rhodococcus*.

Microbes from the genus *Rhodococcus* have also been classified by those of skill in the art as belonging to the genus *Nocardia* as disclosed by the ATCC Catalog of Bacteria and Bacteriophages.

Some microbe belonging to the genus *Nocardia* have been reclassified as belonging to the genus *Rhodococcus*. Therefore, because of the cross-classification cross classification of these microbes by those of skill in the art, use of the microbes from the genus *Rhodococcus* to effect the instant biotransformation is considered to be the same as or so closely related as to be obvious over transformation by microbes from the genus *Nocardia* which is clearly a preferred genus in the cited prior art to produce preponderantly either the (R) or the (S) isomer by reduction of the compound of formula 1.

Claims 10, 14, 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over JP 03-285689 [N].

The claims are directed the use of a cultured product or process product of recombinantly produced microbes to enantioselectively produce the (R) isomer of formula 3.

JP 03-285689 discloses the use of an enzyme produced from *Saccharomyces* (Baker's yeast) and NADPH to enantioselectively reduce the instant substrate. Since the instant claims encompass the use of a cultured product or a processed product of the recombinantly engineered microbes and have not disclosed the origin of the genes encoding for the enzymatic activity which have been inserted into the recombinantly engineered microbes, in the absence of evidence to the contrary, the use of a processed product or cultured product of the recombinantly engineered microbe would be the same enzyme product having the same enzymatic activity as employed in the method of JP 03-285689. While the microbes are not the same, the enzyme product would

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be the same or so similar as to be obvious whether produced from the native microbe or from the recombinant microbe containing the genes from the native microbe which encode the enzymatic activity.

The use of the cultured product or processed product of the transformed microbe. because the specification does not disclose from what organisms the genes for the β -keto ester reductase are obtained. For example, if the beta keto ester reductase genes which are inserted into the E. coli host are obtained from *Saccharomyces* (baker's yeast), use of this enzyme alone, free of the yeast is already known in the art to produce the R stereoisomer of the compound of formula 3.

Claim Rejections – 35 USC § 103

Claims 7-9, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,734,367 [A].

The claims are directed to a method for making optically active 3-hydroxy-2-substituted-propionic acid esters comprising: subjecting 2-formylacetic acid ester to a reduction catalyzed by an enzyme source.

The references are relied upon as explained below.

Because the generic portion of US 4,734,367 discloses the use of anaerobic or facultative aerobic yeasts, fungi or bacteria to stereoselectively reduce the compound of formula 2 to the compound of formula 3 (col. 1, l.68) and there are only two possible stereoisomers, (R) and (S), it would have been obvious to use a microbe to reduce the compound of formula II to the compound of formula I because US '367 suggests such stereospecific microbial reduction. Also since the product has only one stereogenic center, it can only be (R) or (S), there are a small number of solutions to the reduction, namely two and the use of a microbe of the recited claim specific genera or species to obtain either the (R) or the (S) stereoisomer reductive product has a reasonable expectation of success given the state of the art and the cited prior art

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reference which suggests such a process. Please note the claims do not require any degree of optical purity for the reactions. Obviousness flows from the recognition of the chemical properties of the substrate and product coupled with recognition of the ability of anaerobic or facultative aerobic yeasts, fungi or bacteria to stereoselectively reduce compound 2 as taught in the cited prior art, in the absence of unexpected results commensurate in scope with the showing.

Claims 17-22, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,734,367 [A] as applied to claims 7-9, 11 above, and further in view of Kido *et al.* [W].

The claims are further directed to the formation of the compound of formula (2) by reacting an acetic acid ester (1) with a base and formic ester and extracting impurities with an organic solvent and transferring (2) into a water layer prior to the microbial reduction.

Kido *et al.* disclose the reaction of an acetic ester derivative (1) with a base and a formic ester to form (2), adding organic solvent and water to the reaction mixture and removing the aqueous layer containing (2), page 5471.

The formation of the substrate (2) of the microbial reduction reaction by reacting an acetic acid ester with a base and formic ester, adding water and organic solvent and removing the organic layer prior to the use of the substrate (2) in microbial reduction methods as disclosed in US 4,734,367, would have been obvious because Kido *et al.* disclose such a reaction to form substrate (2) and US 4,734,367 also teaches that the substrates can be obtained by organic synthesis (col. 5, l. 17).

Claims 10, 14, 16 are rejected under 35 U.S.C. 103(a) as obvious over US 4,734,367 [A] in combination with JP 03-285689 [N].

The claims are directed to the use of a cultured product or processed

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product from a recombinantly product microbe to enantioselectively reduce the compound of formula 2 to the (R) stereoisomer of formula 3.

JP 03-285689 teach the concept of the use of the reductase activity separated from a microbe instead of the microbe itself to reduce the instant substrate.

US 4,734,367 demonstrates a stereoselective fermentative reduction of 2-formylacetic acid ester to (R) or (S) 3-hydroxy-2-substituted propionic acid. Microbes used are preferably aerobic or facultative aerobic yeasts, fungi or bacteria (col. 1, l. 68) and claim 1, preferred microbes belong to the genus *Candida* and other preferred genera, table column 2.

Since the instant claims encompass the use of a cultured product or a processed product of the recombinantly engineered microbes and have not disclosed the origin of the genes encoding for the enzymatic activity which have been inserted into the recombinantly engineered microbes, in the absence of evidence to the contrary, the use of a processed product or cultured product of the recombinantly engineered microbe would be the same enzyme product having the same enzymatic activity as employed by US 4,734,367 in the method taught by JP 03-285689. While the microbes are not the same, the enzyme product would be the same or so similar as to be obvious whether produced from the native microbe or from the recombinant microbe containing the gene(s) from the native microbe which encode the enzymatic activity.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,734,367 [A] in combination with JP 03-285689 [N] as applied to claims 10, 14, 16 above, and further in view of Kido *et al.* [W].

The claims are further directed to the formation of the compound of formula (2) by reacting an acetic acid ester (1) with a base and formic ester and extracting impurities with an organic solvent and transferring (2) into a water layer prior to the microbial reduction.

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Kido *et al.* disclose the reaction of an acetic ester derivative (1) with a base and a formic ester to form (2), adding organic solvent and water to the reaction mixture and removing the aqueous layer containing (2), page 5471.

The formation of the substrate (2) of the microbial reduction reaction by reacting an acetic acid ester with a base and formic ester, adding water and organic solvent and removing the organic layer prior to the use of the substrate (2) in microbial reduction methods as disclosed in US 4,734,367, would have been obvious because Kido *et al.* disclose such a reaction to form substrate (2) and US 4,734,367 also teaches that the substrates can be obtained by organic synthesis (col. 5, l. 17).

Claims 12, 15, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,734,367 [A] in combination with JP 03-285689 [N].

The claims are directed to the use of a cultured product or processed product from a recombinantly product microbe to enantioselectively reduce the compound of formula 2 to the (S) stereoisomer of formula 3.

JP 03-285689 teach the concept of the use of the reductase activity isolated from a microbe instead of the microbe itself to reduce the instant substrate.

US 4,734,367 teach the fermentation of a microbe to selectively reduce the instant substrate to the S enantiomer, disclosure at col. 1, l. 68 and claim 1 and example 13.

Since the instant claims encompass the use of a cultured product or a processed product of the recombinantly engineered microbes and have not disclosed the origin of the genes encoding for the enzymatic activity which have been inserted into the recombinantly engineered microbes, in the absence of evidence to the contrary, the use of a processed product or cultured product of the recombinantly engineered microbe would be the same enzyme product

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having the same enzymatic activity disclosed in US 4,734,367 in the method of JP 03-285689. While the microbes are not the same, the enzyme product would be the same or so similar as to be obvious whether produced from the native microbe or from the recombinant microbe containing the genes from the native microbe which encode the enzymatic activity.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,734,367 [A] in combination with JP 03-285689 [N] as applied to claims 12, 15, 16 above, and further in view of Kido *et al.* [W].

The claims are further directed to the formation of the compound of formula (2) by reacting an acetic acid ester (1) with a base and formic ester and extracting impurities with an organic solvent and transferring (2) into a water layer prior to the microbial reduction.

Kido *et al.* disclose the reaction of an acetic ester derivative (1) with a base and a formic ester to form (2), adding organic solvent and water to the reaction mixture and removing the aqueous layer containing (2), page 5471.

The formation of the substrate (2) of the microbial reduction reaction by reacting an acetic acid ester with a base and formic ester, adding water and organic solvent and removing the organic layer prior to the use of the substrate (2) in microbial reduction methods as disclosed in US 4,734,367, would have been obvious because Kido *et al.* disclose such a reaction to form substrate (2) and US 4,734,367 also teaches that the substrates can be obtained by organic synthesis (col. 5, l. 17).

One of ordinary skill in the art would have been motivated at the time of invention to make these substitutions of microbes recited in the claims in order to obtain the resulting compound as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

No claim is allowed.

Response to Arguments

Applicant's arguments filed 1/25/08 have been fully considered but they are not fully persuasive and many are rendered moot by the newly applied rejections.

Applicants argue that the instant claims overcome the prior art citation of US 4,734,367 because the prior art teaches the use of a microbe from the genus *Rhodotorula* to produce the (R) form of formula 3, and that US 4,734,367 does not suggest that the use of a microbe from *Rhodotorula* is capable of producing the S enantioselective reduction.

First, while no microbe from the genus *Rhodotorula* has been exemplified by US 4,734,367 to produce the S enantiomer of (3), the generic portion of the specification states that either (S) or (R) form may be obtained depending on the microorganism used. A preferred genus is *Rhodotorula* (col. 3), while the exemplified *Rhodotorula*, *Rhodotorula glutinis* has (R) enantioselectivity, the use of any microbe from *Rhodotorula* to make either the (R) or the (S) form of (2) is taught in the generic disclosure and encompassed by claim 1.

Second, applicants' arguments are not commensurate in scope with their showing which demonstrates only certain species of *Rhodotorula* have (S) enantioselectivity, while other species have (R) enantioselectivity. This appears to also be the generic teaching of the prior art reference. Since a species of *Rhodotorula*, is capable of either (R) or (S) enantioselectivity, see Table 1 of the instant specification and Example 2 of the cited prior art, it appears that enantioselectivity is a strain dependent characteristic. Thus, the urgings of applicants are not commensurate in scope with the claims.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is

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applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651